Functional Magnetic Resonance Imaging

Peter A. Bandettini, Ph.D.

Section on Functional Imaging Methods and The Functional MRI Facility,

National Institute of Mental Health, National Institutes of Health

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(Eds. Carl Senior, Tamara Russell, Michael Gazzaniga)

Correspondence to:

Peter A. Bandettini, Ph.D.

Chief, Section on Functional Imaging Methods

Director, Functional MRI Facility

National Institute of Mental Health

Building 10, Room 1D80

10 Center Dr. MSC 1148

Bethesda, MD 20892-1148

bandettini@nih.gov

Introduction

The idea of using Magnetic Resonance Imaging to assess human brain activation non-invasively, rapidly, and with relatively high spatial resolution, was, before 1990, pure fantasy. The arrival of functional MRI (fMRI) was marked by the publication of the groundbreaking paper by Belliveau et al. in November of 1991 (Belliveau et al., 1991). While it was innovative and generated a large amount of excitement, the technique itself, involving two bolus injections of Gadolinium-DTPA to characterize blood volume changes with activation, was essentially rendered obsolete as a brain activation assessment method by the time it was published. It was replaced by a completely non-invasive MRI-based technique utilizing endogenous functional contrast associated with localized changes in blood oxygenation during activation.

Between the early spring and late fall of 1991, the first successful experiments were carried out at the Massachusetts General Hospital (May, 1991), University of Minnesota (June, 1991), and Medical College of Wisconsin (Sept, 1991) using endogenous MRI contrast to assess brain activation. These experiments were published within two weeks of each other in the early summer of 1992.

The mechanism of endogenous contrast by which results were based was pioneered by Ogawa et al (Ogawa et al., 1990), who coined the term Blood Oxygenation Level Dependent (BOLD) and Turner et al (Turner et al., 1991), who discovered the contrast while searching for changes in diffusion coefficient with apnea. In a prescient quote in 1990 – two years before the first successful experiments were published and about a year before the first successful experiments were performed, Ogawa et al predicted the beginning of a new brain activation method (Ogawa et al., 1990):

"BOLD contrast adds to…functional MRI methodologies that are likely to be complementary to PET imaging in the study of regional brain activity."

When researchers found that, in fact, BOLD signal increased with an increase in brain activation, evidence was found in the Positron Emission Tomography (PET) literature (Fox and Raichle, 1986) from several years earlier demonstrating an activation-induced decrease in oxygen extraction fraction, therefore predicting an increase in MRI signal with activation.

Another non-invasive fMRI technique that emerged almost simultaneously with BOLD fMRI is known as arterial spin labeling (ASL) (Williams et al., 1992). The contrast in ASL arises from blood flow and perfusion, independent of blood oxygenation. Other techniques, allowing non-invasive assessment of activation-induced changes in blood volume (Lu et al., 2003) and oxidative metabolic rate (Davis et al., 1998, Hoge et al., 1999) have since been developed. BOLD fMRI is currently the brain activation mapping method of choice for almost all neuroscientists because it is easiest to implement and the functional contrast to noise is a factor of two to four higher than the other methods. Functional contrast to noise (defined as the signal change / background fluctuations) ranges from 2 to about 6 at higher field strengths if BOLD contrast is used. Currently, the need for sensitivity outweighs the need for specificity, stability over long periods of time, quantitation, or baseline state information – all which are advantages inherent to ASL, and all which come at the price of sensitivity.

Since these first discoveries, advancements in hardware, methodology, signal interpretability, and applications have been synergistically evolving over the past 14 years. Hardware includes magnetic field strength, radiofrequency coils, and subject interface devices. Methodology includes pulse sequences, post processing, multi-modal integration, and paradigm design. Signal interpretability includes advancements in understanding the relationship between underlying neuronal activity and BOLD obtained use of simultaneous direct measures of neuronal activity as well precise modulation of neuronal activity dynamics and magnitudes. Applications include not only those directed at understanding brain organization but also towards complementing clinical diagnoses and characterizing neurological and psychiatric disorders. Generally, advances in any one of these domains have enabled further advances in the others, while the needs of one domain have in many instances driven the development of the others. This highly interdisciplinary and exciting co-evolution will be described in the Development section of this chapter.

Even though fMRI is about 14 years old, unknowns remain regarding the physiological and biophysical factors influencing fMRI signal changes. New insights into the principles of BOLD and other fMRI contrast mechanisms as well as image acquisition and post processing are published at a steady rate. In the Principles section of this chapter, the latest information regarding the acquisition, processing, and interpretation of fMRI signal changes is described.

Functional MRI is continually being shaped by these innovations in hardware, methodology, interpretation, and applications. Scanner field strength and image acquisitions hardware continues to advance in sophistication – allowing greater sensitivity, speed of acquisition, and resolution. Paradigm design and post processing methods continually emerge as applications demand. New methods for integrating fMRI with other brain activation assessment techniques have emerged allowing more precise interpretation of fMRI signal changes as well as introducing new novel applications. Most applications remain in the brain research domain, but fMRI is currently poised at the cusp of making an impact clinically as robustness and interpretability increase and as differences in fMRI signal changes characteristics (activation maps and signal change dynamics) of specific patient populations are being characterized. In the Development section, all of the above topics are covered. In addition a sampling of highlights of fMRI development is described.

The sources of contrast in functional MRI – cerebral blood flow, volume, and oxygenation changes - are secondary to brain activation and therefore place an inherent limitation on the upper spatial resolution, temporal resolution, and interpretability of the technique. Other limitations of fMRI include sensitivity to subject motion, signal dropout in specific regions, and temporal instability within and across scanning sessions. In the Limitations section, not only will the above issues be described, but also an outline of methods by which these may be overcome are given.

The best fMRI research and applications is being defined by how well the paradigms, processing, and interpretation of results are integrated with other brain function assessment techniques. The insight into human brain function that has been gained by integration with other brain assessment techniques, used either simultaneously or at different times, has been much greater than what fMRI could provide alone. Other techniques that have been successfully integrated with fMRI include behavioral measures, electroencephalography (EEG), magnetoencephalography (MEG), physiologic measurements, optical imaging, electrophysiological measurements, and transcranial magnetic stimulation (TMS). The Integration section will outline the basics of how these other techniques are used in conjunction with fMRI as well as the insights that have been gained.

Lastly, a considerable amount of readily accessible and updated information and tools exist on fMRI. The Further Information section will bullet the most informative fMRI websites and fMRI books published, providing basic information, software, organization information, and course information for the beginner to the most sophisticated user.

Development

When obtaining a perspective of fMRI development, it is important first to put it in context. During 1991, brain activation studies were being performed by a handful of groups using techniques involving ionizing radiation or EEG. While these techniques are still quite useful today, giving complementary information to fMRI, the degree of flexibility offered by fMRI as it came into common use in the early 90's was a huge leap in ease of brain mapping experimentation. Suddenly, after 1992, an investigator could now perform a brain activation study relatively easily: simply put a person in the scanner, have them perform a task during time series image collection, and look for where the MRI changes. This was both a blessing and a curse for the bourgeoning brain mapping community.

This ease of access to these powerful tools contributed to several phenomena: 1. Many poorly planned, executed, and analyzed experiments filled with over-interpretation of artifactual signal changes were published and are still published today, but to a lesser degree as the collective expertise of the imaging community is improving rapidly. As an aside, it is worth mentioning here that the impact of the major fMRI courses offered several times a year for up to 50 people at a time at the Massachusetts General Hospital and Medical College of Wisconsin over the past decade have likely expedited the increase in sophistication of fMRI experimentation and perhaps significantly increased the overall impact of fMRI research over the years. 2. A frantic rush to pick the scientific "low hanging fruit" in functional imaging began in earnest and continues in many contexts today. Most fMRI researchers, myself included, have been caught up in this exciting sense of urgency to use this incredibly powerful technique since it seems that the collective sentiment is that we are only really scratching the surface of its potential. 3. Some truly unique insights into how the human brain is organized, how it changes over time (from seconds to years), and varies across populations have been steadily advanced 4. Most importantly, a much larger collective effort towards using brain mapping technology to understand the human brain and to apply fMRI to diagnosing and treating clinical populations was started. The benefits of the last phenomenon are just beginning to be realized. In 1995, the first meeting devoted to human brain mapping took place in Paris, France due in no small part to the emergence of fMRI. The cornerstone technique of Organization for Human Brain Mapping as well as the Cognitive Neuroscience Society is fMRI.

Picking up in 1992, after the first papers were published, only a handful of laboratories could perform fMRI because it required not only an MRI scanner but the capability of performing high speed MRI – known as echo planar imaging (EPI). EPI is a technique by which an entire image (or "plane") is collected with the use of a single radiofrequency pulse and subsequent signal "echo" – hence the name "echo planar." Typical clinical MRI sequences use over 128 RF pulses for a single image. One pulse typically yields a "line" of data. Because a waiting period is required between RF pulses (the "repetition time" or TR – typically 100 ms to 2 sec), and also because clinical images typically have at least 128 lines, an image collected in this manner takes on the order of several seconds to several minutes. To collect an image with one RF pulse requires that the imaging gradients (that are used to spatially encode the data and thus create an image) are oscillated very rapidly since the usable signal only lasts for about 100 ms. An important point is that not only do these images take time, but their temporal stability (signal fluctuations with repeated collection of the same image) is relatively unstable due to cardiac and respiratory effects producing non-repeatable image artifacts. Collecting an entire image in 30 ms (as with EPI) "freezes" these physiologic processes, causing artifacts to be more or less precisely replicated from image to image over time (with some exceptions) – thus substantially increasing temporal stability. It should be noted that some early studies used non-EPI techniques with some additional artifact correction strategies, but EPI, and more generally, "single-shot" one-RF pulse-per-image techniques are the most common and successful. Until about 1996, the hardware for performing EPI was not available on clinical systems. Centers that performed EPI were those that had home-built low inductance gradient coils or those that were fortunate enough to work in collaboration with small companies that created systems that allowed rapid gradient switching. This type of issue remains today. The most innovative technology for performing fMRI is at least several years ahead of what is available on clinical scanners. The source of this lag time is that fMRI remains a non-clinical technique and vendors choose to apply their research and development efforts elsewhere. This is certain to change as fMRI's clinical utility becomes more apparent.

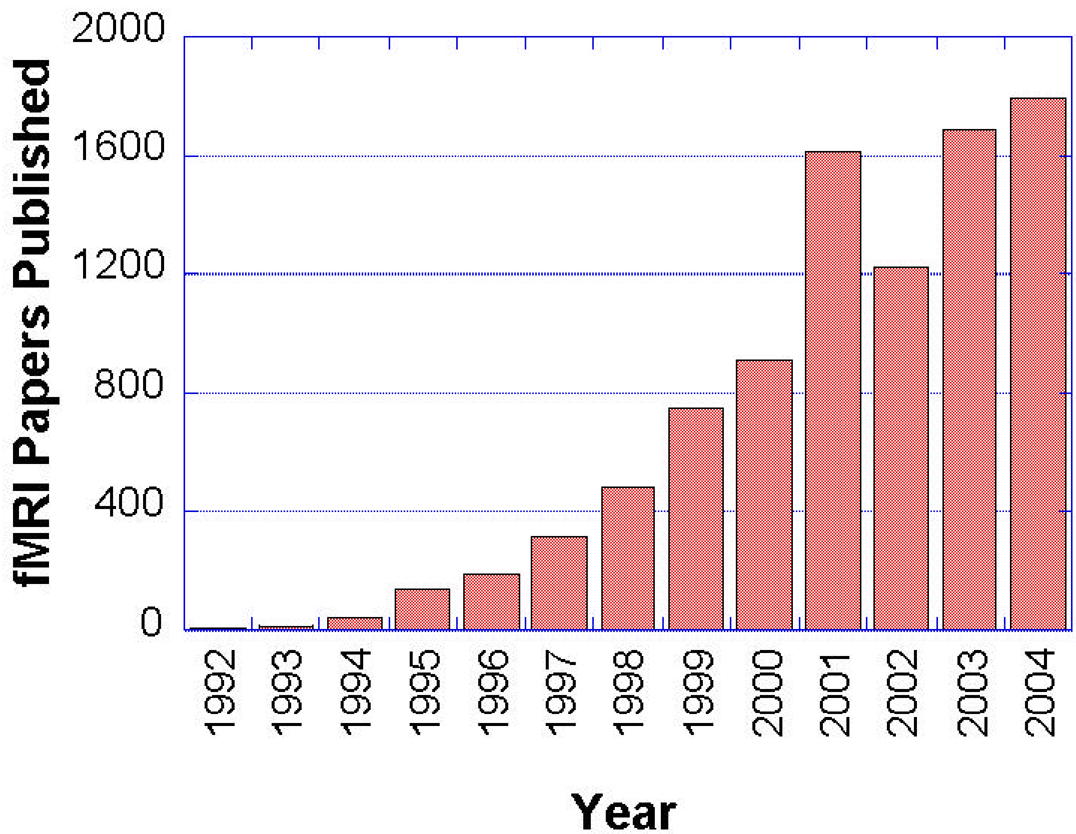

Figure 1: This shows a bar graph of the approximate number of fMRI papers published, as determined by a Medline search of "fMRI" or "functional MRI" after 1993. The growth appears to be exponential until about 2000 and then appears linear.

Figure 1 shows the results of a science citation index reference search on fMRI – related papers published since 1992. The growth appears to be exponential until 2000. It then tapers to a linear function. Papers published before 1996 were typically performed on systems developed in-house. After 1996, the number of groups performing fMRI expanded rapidly. To add a dimension of perspective to this plot, Table 1 shows a list of the 50 papers in fMRI since 1991 that have the highest average citation rate. Listed with the ranking are, average citations per year, total citations (as of Dec 2004), and the year published. In the last column is information of the type of paper published. Application "A" indicates studies which used fMRI to address a specific question in neuroscience.

Method "M" indicates studies which put forth a novel class of fMRI methodology, and Interpretation "I" indicates studies that added useful information regarding the interpretation of fMRI signal changes more accurately. The studies labeled M and A, indicating that they put forth a novel type of method to derive a novel insight into brain organization. It is noteworthy that many of these M/A studies were performed by neuroscientists who have worked closely with individuals who perform methodology development, thus emphasizing the multidisciplinary nature of fMRI and the fact that many cutting edge applications are still tied very closely with advances in methodology. It is noted that since the search criteria was simply "fMRI or functional MRI", many relevant papers were likely missed.

Rank	Cit./Yr.	Tot. Cit.	Yr. Pub.	Authors	Journal, Vol. Pages	Type	Title
1	114	1496	1992	K. K. Kwong, J. W. Belliveau, et al.	PNAS,89,5675-5679	M	Dynamic Magnetic-Resonance Imaging of Human Brain Activity During Primary Sensory Stimulation
2	112	448	2001	N. K. Logothetis, J. Pauls, et al.	Nature,412,150-157	I	Neurophysiological investigation of the basis of the fMRI signal
3	108	537	2000	R. Cabeza and L. Nyberg	Journal of Cog. Neuro.12,1-47	A	Imaging cognition II: An empirical review of 275 PET and fMRI studies
4	84	1095	1992	S. Ogawa, D. W. Tank, et al.	PNAS,89,5951-5955	M	Intrinsic Signal Changes Accompanying Sensory Stimulation - Functional Brain Mapping with Magnetic-Resonance-Imaging
5	82	656	1997	N. Kanwisher, J. McDermott et al.	Journal of Neuroscience,17,4302-4311	A	The fusiform face area: A module in human extrastriate cortex specialized for face perception
6	71	857	1993	P. A. Bandettini, A. Jesmanowicz, et al.	MRM 30,161-173	M	Processing Strategies for Time-Course Data Sets in Functional MRI of the Human Brain
7	67	336	2000	G. Bush, P. Luu et al.	TICS 4,215-222	A	Cognitive and emotional influences in anterior cingulate cortex
8	60	419	1998	C. S. Carter, T. S. Braver, et al.	Science,280,747-749	A	Anterior cingulate cortex, error detection, and the online monitoring of performance
9	58	231	2001	M. F. Egan, T. E. Goldberg et al.	PNAS,98,6917-6922	A	Effect of COMT Val(108/158) Met genotype on frontal lobe function and risk for schizophrenia
10	57	458	1997	J. D. Cohen, W. M. Perlstein, et al.	Nature,386,604-608	M/A	Temporal dynamics of brain activation during a working memory task
11	57	506	1996	R. W. Cox	Comp. and Biomed. Res. 29,162-173	M	AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages
12	55	497	1996	A. Martin, C. L. Wiggs, et al.	Nature 379,649-652	A	Neural correlates of category-specific knowledge
13	53	716	1991	J. W. Belliveau, D. N. Kennedy, et al.	Science,254,716-719	M	Functional Mapping of the Human Visual-Cortex by Magnetic-Resonance-Imaging
14	53	601	1992	P. A. Bandettini, E. C. Wong, et al.	MRM, 25,390-397	M	Time Course EPI of Human Brain Function During Task Activation
15	52	522	1995	M. I. Sereno, A. M. Dale, et al.	Science,268,889-893	M/A	Borders of Multiple Visual Areas in Humans Revealed by Functional Magnetic-Resonance-Imaging
16	50	348	1998	A. D. Wagner, D. L. Schacter, et al.	Science,281,1188-1191	A	Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity
17	50	346	1998	P. J. Whalen, S. L. Rauch et al.	Journal of Neuroscience,18,411-418	A	Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge
18	49	428	1996	K. J. Worsley, S. Marrett, et al.	Human Brain Mapping,4,58-73	M	A unified statistical approach for determining significant signals in images of cerebral activation
19	47	203	2000	M. Corbetta, J. M. Kincade, et al.	Nature Neuroscience,3,292-297	A	Voluntary orienting is dissociated from target detection in human posterior parietal cortex
20	44	174	2001	J. O'Doherty, M. L. Kringelbach, et al.	Nature Neuroscience,4,95-102	A	Abstract reward and punishment representations in the human orbitofrontal cortex
21	44	87	2003	M. F. Egan, M. Kojima, et al.	Cell,112,257-269	A	The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function
22	43	173	2001	P. C. Fletcher and R. N. A. Henson	Brain,124,849-881	A	Frontal lobes and human memory - Insights from functional neuroimaging
23	43	427	1995	R. B. H. Tootell, J. B. Reppas, et al.	Journal of Neuroscience,15,3215-3230	M/A	Functional-Analysis of Human MT and Related Visual Cortical Areas Using Magnetic-Resonance-Imaging
24	42	416	1995	B. A. Shaywitz, S. E. Shaywitz, et al.	Nature,373,607-609	A	Sex-Differences in the Functional-Organization of the Brain for Language
25	42	418	1995	K. J. Worsley and K. J. Friston	Neuroimage,2,173-181	M	Analysis of fMRI Time-Series Revisited - Again
26	41	448	1994	L. Pellerin and P. J. Magistretti	PNAS,91,10625-10629	I	Glutamate Uptake into Astrocytes Stimulates Aerobic Glycolysis - A Mechanism Coupling Neuronal Activity to Glucose-Utilization
27	40	358	1996	H. C. Breiter, N. L. Etcoff, et al.	Neuron,17,875-887	A	Response and habituation of the human amygdala during visual processing of facial expression
28	40	316	1997	J. R. Binder, J. A. Frost, et al.	Journal of Neuroscience,17,353-362	A	Human brain language areas identified by functional magnetic resonance imaging
29	40	317	1997	T. S. Braver, J. D. Cohen, et al.	Neuroimage,5,49-62	M/A	A parametric study of prefrontal cortex involvement in human working memory
30	39	393	1995	M. D'Esposito, J. A. Detre, et al.	Nature,378,279-281	A	The Neural Basis of the Central Executive System of Working-Memory
31	39	391	1995	K. J. Friston, A. P. Holmes, et al.	Neuroimage,2,45-53	M	Analysis of fMRI Time-Series Revisited
32	39	348	1996	G. M. Boynton, S. A. Engel, et al.	Journal of Neuroscience,16,4207-4221	I	Linear systems analysis of functional magnetic resonance imaging in human V1
33	38	348	1996	D. Malonek and A. Grinvald	Science,272,551-554	I/A	Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: Implications...
34	38	384	1995	A. Karni, G. Meyer, et al.	Nature,377,155-158	A	Functional MRI Evidence for Adult Motor Cortex Plasticity During Motor Skill Learning
35	38	114	2002	M. Corbetta and G. L. Shulman	Nature Rev. Neuroscience,3,201-215	A	Control of goal-directed and stimulus-driven attention in the brain
36	38	455	1993	S. Ogawa, R. S. Menon, et al.	Biophysical Journal,64,803-812	I	Functional Brain Mapping by Blood Oxygenation Level-Dependent Contrast Magnetic-Resonance-Imaging...
37	38	303	1997	S. M. Courtney, L. G. Ungerleider, et al.	Nature,386,608-611	M/A	Transient and sustained activity in a distributed neural system for human working memory
38	37	138	2000	J. V. Haxby, E. A. Hoffman et al.	TICS,4,223-233	A	The distributed human neural system for face perception
39	37	443	1993	S. M. Rao, J. R. Binder, et al.	Neurology,43,2311-2318	A	Functional Magnetic-Resonance-Imaging of Complex Human Movements
40	37	368	1995	R. L. Buckner, S. E. Petersen, et al.	Journal of Neuroscience,15,12-29	A	Functional Anatomical Studies of Explicit and Implicit Memory Retrieval Tasks
41	37	365	1995	S. D. Forman, J. D. Cohen, et al.	MRM,33,636-647	M	Improved Assessment of Significant Activation in Functional Magnetic-Resonance-Imaging (fMRI) - Use of a Cluster-Size Threshold
42	36	101	2000	J. B. Hopfinger, M. H. Buonocore et al.	Nature Neuroscience,3,284-291	A	The neural mechanisms of top-down attentional control
43	36	253	1998	W. M. Kelley, F. M. Miezin, et al.	Neuron,20,927-936	A	Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding
44	36	249	1998	M. Corbetta, E. Akbudak, et al.	Neuron,21,761-773	A	A common network of functional areas for attention and eye movements
45	35	317	1996	S. M. Courtney, L. G. Ungerleider, et al.	Cerebral Cortex,6,39-49	A	Object and spatial visual working memory activate separate neural systems in human cortex
46	34	344	1995	J. B. Demb, J. E. Desmond, et al.	Journal of Neuroscience,15,5870-5878	A	Semantic Encoding and Retrieval in the Left Inferior Prefrontal Cortex - a Functional MRI Study of Task-Difficulty and Process Specificity
47	34	271	1997	A. M. Dale and R. L. Buckner	Human Brain Mapping,5,329-340	M	Selective averaging of rapidly presented individual trials using fMRI
48	34	203	1999	K. J. Friston, A. P. Holmes, et al.	Neuroimage,10,385-396	M	Multisubject fMRI studies and conjunction analyses
49	33	305	1999	M. Botvinick, L. E. Nystrom, et al.	Nature,402,179-181	A	Conflict monitoring versus selection-for-action in anterior cingulate cortex
50	33	231	1998	S. M. Courtney, L. Petit, et al.	Science,279,1347-1351	A	An area specialized for spatial working memory in human frontal cortex

Table 1: This shows the 50 papers in functional MRI that have the highest average citation rate per year. (based on science citation search of "fMRI" or "functional MRI." Also shown are the total number of citations for each paper, the authors, journal, and title. The "type" column indicates whether the paper was: "A," an application of fMRI towards a specific neuroscience or clinical question, "M," a paper that primarily focused on a methods development, or "I," a paper that focused on clarifying the relationship between

neuronal activity and functional MRI signal changes. Some papers are combinations of these. The focus of this table is to provide a perspective of the field, as of December 2004, by looking at types of some of the currently most influential papers.

After about 1996, with rapid proliferation of EPI-capable MRI scanners incorporating whole-body gradients, the standard platform for fMRI reached a plateau that is still mostly in use today. The sequence used is gradient-echo EPI, TE: 40 ms, matrix size: 64 x 64, field of view: 24 cm, slice thickness: 4 mm. Typically, whole brain volume coverage using a TR of 2 sec is performed. Time series are typically on the order of 5 to 8 minutes in duration, and a typical experiment involves the collection of about 7 time series per subject scanning session. Multi-subject studies usually settle on assessing about 12 such sessions. Regarding hardware, a whole brain quadrature RF coil is typically used. Around 2002, the "standard" field strength increased from 1.5T to 3T.

Beyond basic collection, standards begin to diverge in that the domains of paradigm design and post processing are still evolving steadily. Nevertheless, "typical" paradigm design methods are either "box-car," involving steady state activation periods for 10 sec or more, or more commonly, "even-related" designs enjoying the flexibility inherent to brief activation periods interspersed within the time series. For processing, SPM is the most common software, but platforms such as Brain Voyager, FSL, and AFNI are almost as ubiquitous. The most common techniques involve the use of "reference" functions for statistical map creation, and when multi-subject data is involved, statistical maps are spatially smoothed and transformed to a standardized space for comparison or averaging.

Recent advances in fMRI data visualization have allowed for unprecedented data navigation and visualization. Illustrated in Figure 2. is how the same fMRI data in its various forms can be simultaneously and interactively visualized. Data were from a retinotopy experiment (expanding ring), processing and visualization performed using AFNI and SUMA (Cox, 1996) surface models were created using FreeSurfer (Dale et al., 1999). The central panel of the figure shows the main controller window of AFNI used to select and manipulate data to be visualized. Figure 2 A, shows EPI time series signal from voxels in the occipital cortex during cyclic visual stimulation. Of the 9 voxels shown here, some show clear modulation at the main frequency of the stimulus while others do not. In Figure 2 B. Statistical maps in color are shown overlaid atop high resolution anatomical data. The colored voxels represent response delay of significantly activated voxels and the cross hair represents the location of the central voxel in panel A. Contours of pial and white/gray matter boundary surface models are shown in blue and red lines. In Figure 2 C a 3D Volume rendering of the data shown in B with cutouts revealing the calcarine sulcus is shown. In Figure 2 D, functional data is projected on models of the same cortical surface with varying degrees of deformation. From left to right we have the white/gray matter boundary surface, an inflated version that reveals buried portions of sulci, a spherical version that can be warped into a standard coordinate space for surface-based group analysis (Fischl et al., 1999, VanEssen and Drury, 1997, Saad et al., 2004) and lastly, a flattened version of the occipital cortex with the data represented in color and relief form. Note that all panels were created simultaneously and interactively. For example, a change of statistical threshold in the main AFNI controller, will affect all displays in panels B through D. A selection of a new location on the flat map in D will cause all other viewers to jump to the corresponding new location. (Figure and caption provided courtesy of Ziad Saad, Ph.D. Statistical and Scientific Computing Core Facility, NIMH).

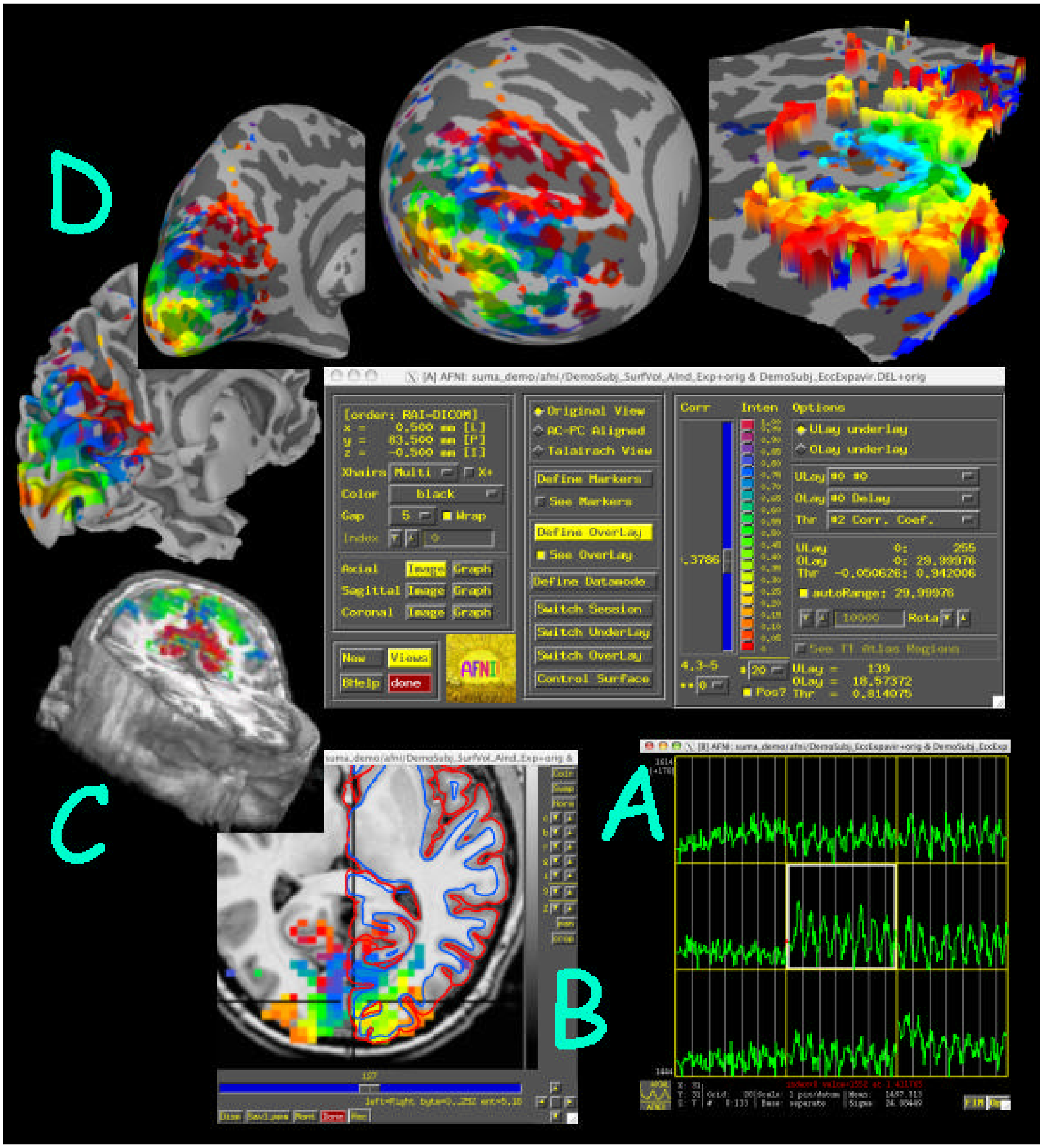

Figure 2: Recent advances in fMRI data visualization allow for unprecedented data navigation and visualization. Illustrated is how the same fMRI data in its various forms can be simultaneously and interactively visualized. Data were from a retinotopy experiment (expanding ring), processing and visualization performed using AFNI and SUMA (Cox, 1996) surface models were created using FreeSurfer (Dale et al., 1999). Central panel- AFNI's main controller window used to select and control data to be visualized. **A.** EPI time series from voxels in the occipital cortex during cyclic visual stimulation. Of the 9 voxels shown here, some show clear modulation at the main frequency of the stimulus while others do not. **B.** Statistical maps in color overlaid atop high resolution anatomical data. The colored voxels represent response delay of significantly activated voxels and the cross hair represents the location of the central

voxel in panel A. Contours of pial and white/gray matter boundary surface models are shown in blue and red lines. **C.** 3D Volume rendering of the data shown in B with cutouts revealing the calcarine sulcus. **D.** Functional data projected on models of the same cortical surface with varying degrees of deformation. From left to right we have the white/gray matter boundary surface, an inflated version that reveals buried portions of sulci, a spherical version that can be warped into a standard coordinate space for surface-based group analysis (Fischl et al., 1999, VanEssen and Drury, 1997, Saad et al., 2004) and lastly, a flattened version of the occipital cortex with the data represented in color and relief form. Note that all panels were created simultaneously and interactively. For example, a change of statistical threshold in the main AFNI controller, will affect all displays in panels B through D. A selection of a new location on the flat map in D will cause all other viewers to jump to the corresponding new location. (Figure and caption provided courtesy of Ziad Saad, Ph.D. Statistical and Scientific Computing Core Facility, NIMH).

Overall, the field of fMRI has been and is punctuated with novel techniques, findings, and controversies. A list of ten out of many developments in fMRI before 2003 is described below to add perspective. Due to limited space, neither this list nor the references associated with each topic are comprehensive.

?? Parametric manipulation of brain activation demonstrated that BOLD contrast approximately followed the level of brain activation: visual system (Kwong et al., 1992), auditory system (Binder et al., 1994), and motor system (Rao et al., 1996).

?? Event-related fMRI was first demonstrated (Blamire et al., 1992). Application of event-related fMRI to cognitive activation was shown (Buckner et al., 1996, McCarthy et al., 1997). Development of mixed event-related and block designs was put forward: (Donaldson et al., 2002). Paradigms were demonstrated in which the activation timing of multiple brain systems timing was orthogonal, allowing multiple conditions to be cleanly extracted from a single run (Courtney et al., 1997).

?? High resolution maps were created: For spatial resolution: ocular dominance columns (Menon et al., 1997, Cheng et al., 2001) and cortical layer activation maps were created (Logothetis et al., 2002). Extraction of information at high spatial frequencies within regions of activation was demonstrated (Haxby et al., 2001). For temporal resolution: Timings from ms to hundreds of ms were extracted (Ogawa et al., 2000, Menon et al., 1998, Henson et al., 2002, Bellgowan et al., 2003).

?? The development of "deconvolution" methods allowed for rapid presentation of stimuli (Dale and Buckner, 1997).

?? Early BOLD contrast models were put forward: (Ogawa et al., 1993, Buxton and Frank, 1997). More sophisticated models were published that more fully integrated the latest data on hemodynamic and metabolic changes (Buxton et al., 2004).

?? The use of continuous variation of visual stimuli parameters as a function of time was proven a powerful method for fMRI-based retinotopy: (Engel et al., 1994, Deyoe et al., 1994, Sereno et al., 1995).

?? The development of "clustered volume" acquisition was put forth as a method to avoid scanner noise artifacts: (Edmister et al., 1999).

?? The findings of functionally related resting state correlations: (Biswal et al., 1995) and regions that consistently show deactivation (Binder et al., 1999, Raichle et al., 2001) were described.

?? Observation of the pre-undershoot in fMRI (Hennig et al., 1997, Menon et al., 1995, Hu et al., 1997) and correlation with optical imaging was reported (Malonek and Grinvald, 1996).

?? Simultaneous use of fMRI and direct electrophysiological recording in non-human primate brain during visual stimulation elucidated the relationship between fMRI and BOLD contrast. (Logothetis et al., 2001). Simultaneous electrophysiological recordings in animal models revealed a correlation between negative signal changes and decreased neuronal activity (Shmuel et al., 2002). Simultaneous electrophysiological recordings in animal models provided evidence that inhibitory input could cause an increase in cerebral blood flow (Matheiesen et al., 1998).

?? Structural equation modeling was developed in the context of fMRI time series analysis: (Buchel and Friston, 1998).

As mentioned, this list is only a sampling of the tremendous amount of novel work establishing fMRI as an powerful tool for investigating and quantitating human brain activity. More recent, ongoing, and future innovations and issues in fMRI will be described in the Innovations section.

Principles

Several types of physiologic information can be mapped using fMRI. As described in the introduction, this information includes baseline cerebral blood volume (Rosen et al., 1991), changes in blood volume (Belliveau et al., 1991, Lu et al., 2003), quantitative measures of baseline and changes in cerebral perfusion (Wong et al., 1999), changes in blood oxygenation (Bandettini et al., 1992, Blamire et al., 1992, Frahm et al., 1992, Kwong et al., 1992, Ogawa et al., 1992), resting state oxygen extraction fraction (An et al., 2001) , and changes in $CMRO_2$ (Davis et al., 1998, Hoge et al., 1999).

BOLD Contrast:

The basic mechanism for BOLD signal changes with brain activation is described. During resting state, blood oxygenation in capillaries and veins is lower than that of arteries due to the resting state extraction of oxygen from the blood. Deoxyhemoglobin (deoxy-HB) is paramagnetic relative to the rest of brain tissue and water and oxyhemoglobin (oxy-Hb) has the same susceptibility as brain tissue and water. An object (in this case, a deoxy-Hb molecule or a capillary or vein containing deoxy-Hb molecules) that has a different susceptibility than its surrounding medium creates a magnetic field distortion when placed in a magnetic field. Water molecules (the primary signal source in MRI), also called “spins,” precess at a frequency that is directly proportional to the magnetic field that they are experiencing. Within a voxel, if spins are precessing at different frequencies, they rapidly become out of phase. The MRI signal is directly proportional to the coherence of spins. If they are completely out of phase, destructive addition takes place and there is no signal. If they are completely in phase, there is maximal signal. During resting state, a large enough fraction of spins are out of phase, due to the many microscopic field distortions in each voxel, causing the MRI signal to be attenuated somewhat relative to if there were no deoxy-Hb present. During activation, blood flow increases locally such that there is an overabundance of oxygenated blood delivered to the active regions. The reason for this is still not fully understood. This causes the amount of deoxy-Hb to decrease and therefore, the magnitude of the magnetic field distortions to decrease as well, thus increasing the coherence of spins within each voxel, leading to a signal increase of a few percent.

This signal begins to increase approximately two seconds after neuronal activity begins, and plateaus in the 'on' state after about 7 to 10 seconds. A pre-undershoot is sometimes observed and a post-undershoot is more commonly observed. These effects are likely due to transient mismatches between either blood volume or $CMRO_2$ before and after respective increases and decreases in flow occur. The dynamics, location, and magnitude of the signal are highly influenced by the vasculature in each voxel. If voxels happen to capture large vessel effects, the magnitude of the signal may be large (up to an order of magnitude larger than capillary effects), the timing a bit more delayed than average (up to 4 seconds delayed from capillary effects), and the location of the signal somewhat distal (up to a centimeter) from the true region of activation. While improvements are being made in fMRI methodology such that the effects of this variability are kept to a minimum, the problem of variable vasculature and hemodynamic coupling in fMRI nevertheless remains at all field strengths and limits the depth and range of questions that can be addressed using fMRI.

Perfusion Contrast::

Introduced nearly simultaneously with BOLD functional MRI methods was the noninvasive method for mapping perfusion in the human brain, known as arterial spin labeling (ASL). The technique generally involves applying a radiofrequency pulse (or continuous RF excitation) below the imaging plane (in the neck area). If there were no blood flow, the magnetization that was applied would simply decay and not influence the signal where the images were being collected. With flowing blood, the altered magnetization of the "labeled" blood affects the longitudinal magnetization (T1) in the imaging slices as it flows in and as water spins mix and exchange magnetization in the imaged brain tissue. A second set of images are obtained either with the label applied above the brain or not applied at all. Therefore this second image is not affected in the same manner by magnetization of inflowing spins. The last step is to perform pairwise subtraction of the two images, removing all the anatomical signal from each image, leaving behind only the effect on the signal by the label. Because of the low signal to noise inherent to this type of contrast, an average of typically several hundred "label-minus-no label" pairs are obtained to create a map of baseline perfusion.

A strong determinant of perfusion contrast with this technique is the time, known as TI, between the labeling pulse and the subsequent image collection. If the TI is 200 ms, only the effects of the most rapidly flowing blood is observed (typically arteries). As the TI approaches 1 second, slower perfusing spins in and around capillaries appear. Beyond 1 second, the magnetization of the label decays significantly. A time series of these "label-minus-no label" pairs can be collected for the purpose of functional imaging of brain activation. ASL has not achieved the success of BOLD functional MRI mostly because of limitations in the number of slices obtainable, temporal resolution, and decreased functional contrast to noise of the technique relative to BOLD fMRI. Nevertheless, its superior functional specificity and stability over long periods of time, along with quantitative information, have made it useful for many applications where BOLD fMRI falls short.

Sensitivity

A primary struggle in fMRI is to increase sensitivity. This is achieved by increasing the magnitude of the signal change or decreasing the effects of noise. This struggle has also been the impetus for imaging at ever higher field strengths. With an increase in field strength, signal to noise increases proportionally and both BOLD and perfusion contrast increase (BOLD due to greater changes in transverse relaxation changes with activation and perfusion due to increases in T1 of blood, which allows the magnetization of the labeled blood to remain longer). The difficulties with going to higher field strength, aside from system instabilities, and generally worse quality at the base of the brain due to greater effects of poor shimming, are that physiologic fluctuations increase as well. Methods for removing these fluctuations remain imperfect. That said, a primary advantage of imaging at higher field strengths (i.e. 7 T) is that the lower limit of signal to noise is achieved with a much smaller voxel volume, thus allowing much higher imaging resolution (down to 1 mm^3) at comparable functional contrast levels as imaging at 3T with voxel volumes of 3 mm^3. This increase in resolution without prohibitive losses in sensitivity has likely been what has allowed imaging of ocular dominance column activation at 4T but not at lower field strengths. Currently, successful results in imaging humans have been obtained at 7 T(Vaughan et al., 2001, Pfeuffer et al., 2002b, Yacoub et al., 2001). It is certain that these will multiply rapidly.

Radiofrequency coils can also be used to increase sensitivity and resolution. The development of RF coil, pulse sequence, and receiver technology will be discussed below in the Innovation section.

Other processing steps for increasing sensitivity may include temporal and spatial smoothing. Because of the inherent temporal autocorrelation in the signal (from hemodynamics or other physiological processes) temporal smoothing is performed so that the temporal degrees of freedom may be accurately assessed. Spatial smoothing can be performed if high spatial frequency information is not desired and as a necessary pre - spatial normalization step (matching effective resolution with the degree of variability associated with spatial normalization techniques) for multi-subject averaging and comparison. An often overlooked fact is that higher temporal sensitivity (and less image warping due to a shorter readout window) is achieved by collecting the images at the spatial resolution initially desired rather than spatially smoothing the maps after data collection. In many instances, spatial smoothing is not desired – particularly when high spatial frequency information in individual maps is compared (Haxby et al., 2001).

Once images are collected, voxel-wise time series analysis is carried out after motion correction is performed. Typically, a model function or functions are used as regressors, and the significance of the correlation of the time series data with the regressors is calculated on a voxel-wise basis. If the expected activation timing is not known, more open ended approaches to analysis, such as independent component analysis (ICA) (Beckmann and Smith, 2004), are performed.

Innovation

The quantity and impact of fMRI innovations, and the proportion of truly high quality work in fMRI, has continued to grow as the field has matured, rendering any effort to stay abreast of the latest and the most interesting advances nearly an impossible task. While the above Development section has touched upon a few of the major innovations over the last 14 years, this section will highlight even fewer examples of emerging innovations that could either pan out and make a major impact or be relegated to something that almost worked. The goal is not to predict what will succeed but to give a sense of the vibrancy of the field, always having the potential for expanding in new exciting directions.

The innovations touched upon in this section include those in imaging technology, experimental design to data collection to analysis, potentially novel clinical applications, and a potentially novel contrast mechanism.

Imaging Technology

A set of recent developments in acquisition hardware and imaging strategy may allow fMRI to be taken to a new level of sensitivity and/or resolution and/or speed. A typical acquisition uses a single quadrature whole brain RF coil feeding into one acquisition channel, and collects single shot EPI data at 64 x 64 resolution. Recently, the ability to acquire MR data with simultaneous multiple high bandwidth channels (Bodurka et al., 2004), feeding in from multiple RF coils, has enabled, above all, a jump in image signal to noise ratio. Figure 3 demonstrates the gains in sensitivity with multiple RF coils Sensitivity is approximately proportional to the size of the RF coil used. In the past, some studies chose to sacrifice brain coverage for sensitivity by using a single "surface" RF coil for acquisition. Today, the use of multiple small RF coils covering the entire brain allows full brain coverage and significantly higher sensitivity than one large coil. Recently, a 32 RF coil device has been constructed at the Massachusetts Hospital Group for brain imaging, leading to an increase in signal to noise by up to a factor of 6 for an individual image, but when taking into consideration unfilterable physiologic noise, the gains are likely to be only about a factor of 3. Currently, it is not certain what the optimal number of coils is with regard to increases in sensitivity

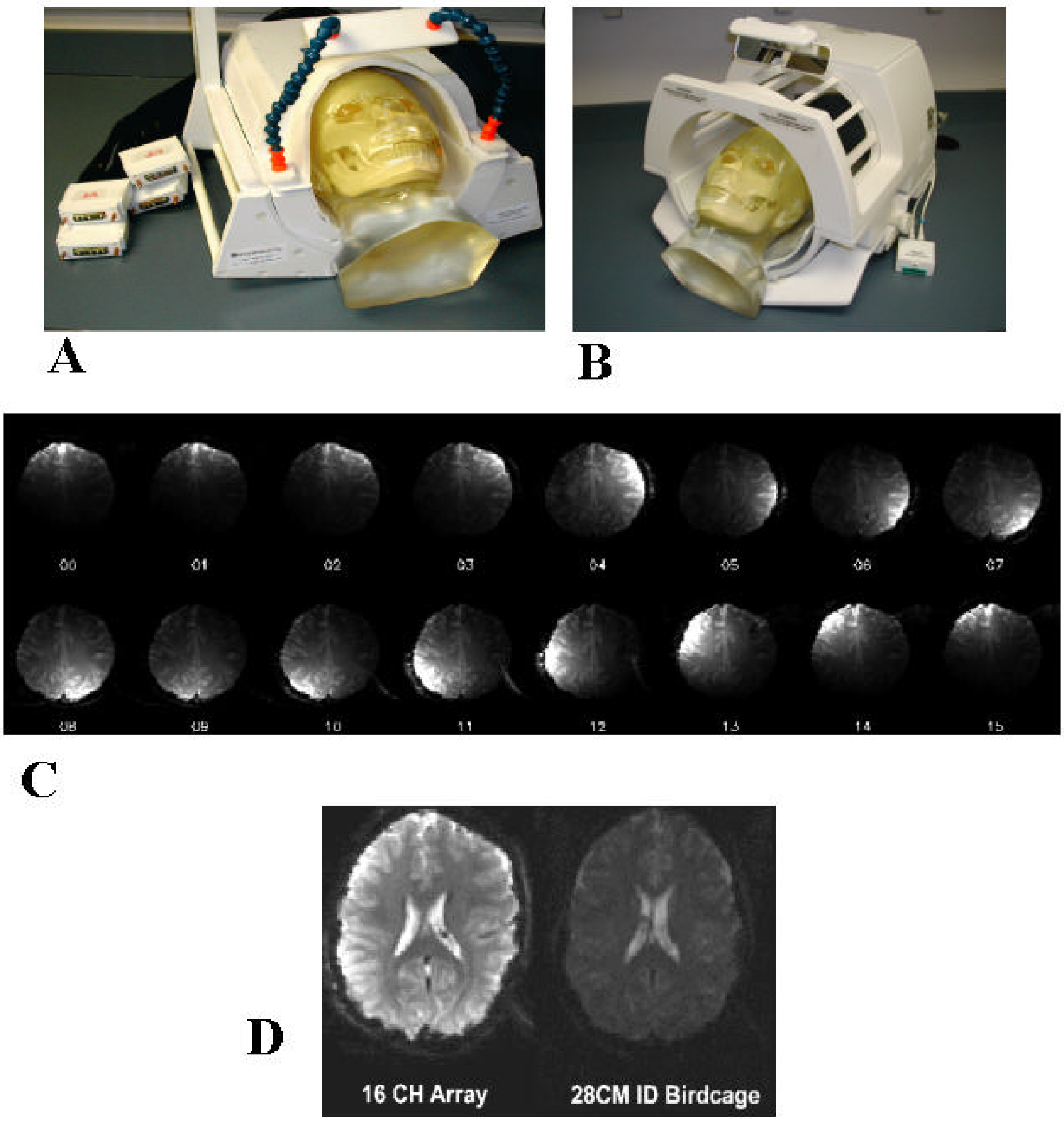

Figure 3: This is a comparison of image signal intensity of MR images created with **A.** a 16 channel RF coil system (NOVA Medical RF coil combined with NIH in-house parallel acquisition system- ref). and **B.** A single channel quadrature RF coil (GE Medical Systems). Each of the 16 small RF coils within the NOVA Medical RF coil has distinct region of sensitivity as shown in **C.** The most straightforward manner to combine this data is by simple addition after reconstruction. In **D**, the image on the left was created by addition of the 16 individual images in C. The image on the right was created from the GE Medical Systems quadrature RF coil. The two images being compared have been normalized such that the noise levels match. The signal intensity therefore gives a relative measure of signal to noise. (Figure provided courtesy of Jerzy Bodurka, Ph.D. Functional MRI Facility. The NOVA Medical 16 channel coil was designed by Jeff Duyn, Ph.D., Section on Advanced MRI, NINDS).

A second use of multi-channel acquisition, aside from increasing signal to noise, is in conjunction with a novel image acquisition/reconstruction strategy that uses the spatially distinct sensitive region of each RF coil to help spatially encode the data – with a small cost in signal to noise. This strategy is known as SENSE imaging (SENSitivity Encoding) (de Zwart et al., 2002). By using the coil placement to aid in spatial encoding, less time is necessary for encoding the spatial information of the data to create an image of a given resolution. This advantage can be used in two ways. First, the readout window width can be remain the same as without SENSE but the image resolution can be increased substantially. Second, the image resolution can remain the same but the width of the readout window can be decreased substantially. This reduction in readout window width allows a small increase in the number of EPI slices to be collected in a TR, therefore allowing a reduction in TR for a given number of slices, more slices for a given TR (allowing thinner slices perhaps), or an increase in brain coverage for a given TR (if a shorter TR had previously limited brain coverage). Incorporating this imaging strategy at field strengths above 3T may allow robust single shot 1 mm^3 matrix size EPI with a high enough signal to noise for fMRI.

Free behavior and natural stimuli paradigms

A second innovation direction is in the domain of paradigm design strategies. An ongoing challenge in fMRI is that of having the subject perform a task in a predictable and repeatable manner. This is not only not possible in many instances but limits the type of questions that can be addressed using fMRI. One common solution to this, as described in the Integration session below, is to keep track of the responses of the subject to specific tasks, then perform post-hoc data averaging based on the responses. A potentially powerful extension of this idea is to collect a continuous measure of the subject's behavior. In this manner, a natural parametric variation in the response parameters may be used to guide data analysis. Any continuous measure would suffice. The subject simply has to move a joystick or track ball or have their eye position or skin conductance monitored. They could be following an object, determining certainty, expectation, anxiety or subjective perception of motion, etc.. The way that this data can be used is to calculate the moment to moment measurement and use it as a regressor in the analysis.

Related to this type of natural paradigm is the use of natural stimuli: viewing a movie for example. Regressors can be calculated from various salient aspects of the movie presentation such as color, motion, volume, speech, or even the interaction of continuously-measured eye position with these variables. A study involving movie viewing was recently published (Hasson et al., 2004) in which a highly novel processing technique, tailored to paradigm, was used. This technique was based on the understanding that, because the movie had many variables changing in an unpredictable manner it was difficult to generate a set of reference functions for determining the similarly activated regions across subjects. What was done instead was to play precisely the same movie sequence at least twice for each subject and across all subjects. The assumption was that a distinct, repeatable temporal pattern would be manifest. The correlation in the time series fMRI was determined across subjects rather than attempting to choose an appropriate ideal reference function and compare subsequent activation maps. This is also an effective technique to apply for the same subject across identical time series collections(Levin and Uftring, 2001), as it makes no assumption about what the data should look like – only that it shows a repeatable change.

Real time fMRI incorporating feedback to the subject

A technical challenge in fMRI is to perform basic analysis on data as it is being collected (Cox et al., 1995). This approach is important for several reasons. A primary practical reason is to ensure data quality during the scan. This, in fact, is likely to be a necessary requirement in order for fMRI to be incorporated into daily clinical practice. A secondary reason that is just beginning to be explored is that of allowing the scanner or the subject being scanned to guide experimental process in real time. A couple of truly unique twists on this avenue have recently been advanced. First, it has been determined that if a measure of brain activation in specific regions activated by a cognitive task (not sensorimotor) is fed back to the subject being imaged, the subject can learn, subjectively, to either increase or decrease the level of activation (Weiskopf et al., 2003). This finding offers the fascinating possibility of humans interacting directly with and through computers through simple thought process regulation. As a demonstration of this technique, this research group has trained subjects to play “pong” using mental control of a “paddle” in which the vertical location was simply proportional to the degree of activation in the controllable brain regions being activated. Using two scanners collecting data simultaneously, subjects are able to successfully play “brain pong” using subjective control of their fMRI signal changes.

A second application of this type of subjective control has been reported by DeCharms et al. (DeCharms et al., 2004). In this study by their group, patients experiencing chronic pain were instructed to reduce the fMRI signal intensity in regions that were determined in a previous experiment to be associated with pain perception. As in the “brain pong” experiment, the subjects were provided with feedback regarding the level of fMRI signal in these regions and were instructed to use whatever strategy they could come up with to decrease the signal. Not only did the experiment result in a subjective decrease in pain perception for most subjects, but this effect apparently lasted months after the experiment was carried out.

Direct Neuronal Current Imaging

A hope among brain imagers would be to possess a technique that would allow direct mapping of brain activity with spatial resolution on the order of a cortical column *and* temporal resolution on the order of an action potential or at least a post synaptic potential. Recent work has established that, in ideal conditions, the minimal magnetic field change detectable with MRI is on the order of 0.1 nT (Bodurka and Bandettini, 2002). Approximate calculations based on MEG measurements of 100 fT at the surface of the skull, estimate the magnetic field surrounding a dipole is also on the order of 0.1 nT. An increase in neuronal activity should be manifest as a highly localized and extremely transient MRI signal magnitude decrease and/or MRI phase shift (Bandettini et al., in press). Experimental results from groups attempting to detect this effect in humans have been mixed but some have claimed success (Konn et al., 2004, Xiong et al., 2003). Even if this technique proves feasible, its utility will likely be limited, at least initially, by the small size of the magnitude of the effect and the relatively small range of experiments possible using it due to the necessity for specific time-locked averaging. Nevertheless, it is difficult to predict the ultimate success of this novel contrast mechanism since research efforts towards this goal have only begun.

Limitations

The limitations of fMRI towards accurately assessing brain activation are fundamentally determined to two major factors: 1. the method by which images are collected, and 2. the relationship between neuronal activity and hemodynamic changes. This section will describe the temporal, spatial, and interpretative limits of fMRI.

Temporal Resolution

Echo planar images typically have an acquisition time of 30 ms. Assuming an echo time of 40 ms (the center of the readout window), data acquisition ends after 55 ms. About 15 ms is usually required for gradients to be applied at the end of the sequence to eliminate remaining magnetization and for fat saturation to be applied at the beginning. The total time per plane for single-shot EPI time series collection is therefore about 65 ms, allowing for about 15 images to be collected in a second. For volume collection, typically consisting of 30 slices, a TR of 2 sec is therefore required. It is also possible to collect one image (as opposed to multiple images in a volume) at a rate of 15 images per second over time.

As described, the hemodynamic response behaves like a low pass filter for neuronal activity: At on / off frequencies of 6 sec on / 6 sec off (0.08 Hz), BOLD responses begin to be attenuated relative to longer on / off times. At on / off frequencies of 2 sec on / 2 sec off (0.25 Hz) the BOLD response is almost completely attenuated. Even though BOLD attenuates these rapid on / off responses, activity of very brief duration can be observed. Activity durations as low as 16 ms have been shown to cause robust BOLD signal changes indicating that there is no apparent limit to the briefness of detectible activation. It is also heartening that when performing repeated experiments, the hemodynamic response in each voxel shows only a variability on the order of 100 ms.

A desire in functional brain imaging is not only to spatially resolve activated regions but also to determine the precise timing of activation in these regions either relative to the stimulus or input but also relative to each other. The temporal resolution required for this type of assessment is on the order of at least tens of milliseconds. With BOLD contrast, the latency of the hemodynamic response has a range of 4 seconds due primarily to uncharacterized spatial variations in underlying hemodynamics or neurovascular coupling from voxel to voxel even within the same region of activity. If a voxel contains mostly larger venous vessels, the response is typically more delayed than if the voxel captures predominantly capillaries. This observation is only approximate. The precise reasons for latency variations are still not completely determined.

Methods have been proposed to alleviate this problem. The most direct is to try to identify larger vessels by thresholding based on percent signal change or temporal fluctuation characteristics. The accuracy of these methods remains undetermined. Another solution is to use pulse sequences sensitive only to capillary effects. Arterial spin labeling techniques are more sensitive to capillaries, but the practical limitations of lower functional contrast to noise and longer inter – image waiting time (due to the additionally required TI of about 1.5 sec) make this unworkable for most studies. Spin-echo sequences performed at very high field strengths or with velocity nulling gradients (both which eliminate intravascular large vessel effects) are also sensitive to capillary effects, but the reduction in functional contrast to noise is about a factor of 2 with spin-echo, and an additional factor of 3 with velocity nulling gradients to remove intravascular signal, likely rendering the contrast too low to be useful.

An alternate strategy is to focus on localized *changes* in latency and width with task timing changes. As mentioned, within a voxel, the hemodynamic response varies on the order of 100 ms allowing significantly more accurate assessment if activation timing varies within a region. When using a task modulation that causes a difference in reaction time, one region of the brain shows an increase width and another shows an increase delay, then it can be inferred that the region showing the width change is spending additional time to process information and the region showing the increased delay is downstream from the region showing the width change, having to wait until processing was complete in that node in order to receive any information. This is an oversimplified model but illustrates how temporal information may be extracted in fMRI. The key is task timing modulation and observation of hemodynamic changes on a voxel-wise basis.

Figure 4 shows an adaptation from (Bellgowan et al., 2003) illustrating the point made above. The subject performed a word recognition task in which the stimuli included non-words and words. The task also involved presentation of words and non-words at at varying rotation angles. It has been observed that that it takes longer to recognize non-words than words. It also takes longer to identify the word if it is rotated. The hypothesis is that the region performing word rotation and word recognition are likely to be spatially distinct. Figure 4 shows average time courses from the left anterior prefrontal cortex – typically associated with word generation. It appears that when comparing word vs non-word processing, the width of the hemodynamic response is wider by about 500 ms, suggesting that there is longer duration of activity in this region during the non-word recognition process. When comparing rotation angle, the onset of activation in this region appears delayed as a function of angle of rotation, suggesting that this region is "downstream" from the area performing the processing necessary to rotate the words, which appear to have to be first rotated before the information is passed on to the left anterior prefrontal cortex.

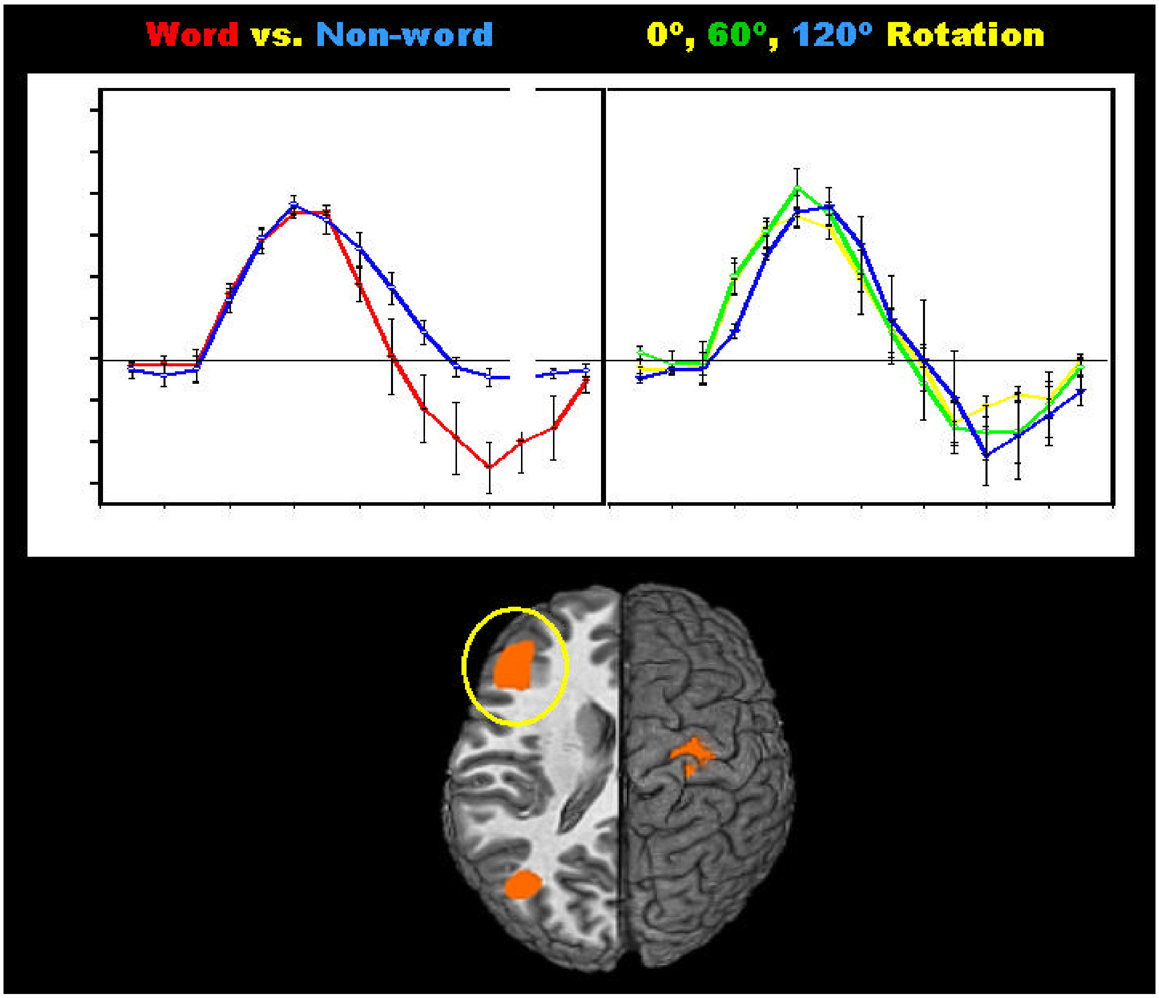

Figure 4: Adapted from (Bellgowan et al., 2003). This shows the averaged time courses from the left anterior prefrontal cortex during a word recognition task in which the words were presented at varying rotation angles. When the subject is comparing word vs non-word processing, the width of the hemodynamic response is wider by about 500 ms, suggesting that there is longer duration of activity in this region during the non-word recognition process. When comparing rotation angle, the onset of activation in this region appears delayed as a function of angle of rotation, suggesting that this region is "downstream" from the region associated with word rotation.

Lastly, discussed in the Integration section, is the combined use of fMRI and MEG to potentially allow accurate assessment of cascaded activity across nodes of a network.

Spatial Resolution

The upper in–plane resolution of standard single shot EPI is about 2 mm^2. The use of multi-shot EPI (at a cost of time and stability) or more recently conceived of strategies incorporating multiple RF coils to aid in spatial encoding of data (discussed in the Innovation section), can allow functional image resolutions of about 1mm^3.

As with temporal resolution limits, the spatial resolution limits are predominantly determined not by limits in acquisition but by the spatial spread of oxygenation and perfusion changes that accompany focal brain activation. This “hemodynamic point spread function” has been empirically determined to be on the order of 3 mm^3 (Engel et al., 1997) but the effects of draining veins have been observed to be as distal as 1 cm from focal regions of activation identified using perfusion contrast.

The pulse sequence solutions for dealing with the variations in hemodynamics are similarly applicable as those for temporal resolution limits. In addition, spatial calibration methods have been proposed involving hypercapnia comparisons (Bandettini and Wong, 1997, Cohen et al., 2004) In spite of these limitations and limited solutions, ocular dominance column (1mm^3) (Cheng et al., 2001, Goodyear and Menon, 2001) and cortical layer (<0.5mm^3) (Logothetis et al., 2002) delineation have been achieved using BOLD, perfusion based, and blood volume based methods. With BOLD contrast, which is thought to have the lowest resolution, columnar and layer specificity was only achieved by subtraction of activation from tasks activating interspersed yet distinct regions (i.e.

columns or layers). Without this subtraction step, this resolution was not able to be obtained. An ongoing issue with regard to the upper resolution of fMRI is whether or not *fine* delineation necessarily translates to *accurate* delineation – meaning that detailed activation maps may not necessarily precisely registered with underlying function. This remains to be demonstrated using a gold standard.

Interpretation

Considerable effort has been directed towards understanding the precise relationship between fMRI signal changes and neuronal activity. Strategies for investigating this have included: 1. Animal models and the simultaneous use of other measures of neuronal activity such as multi-unit electrodes or more precise measures of hemodynamic changes, such as optical imaging 2, Parametric modulation of magnitude or timing of activation in humans with corresponding measurement of fMRI signal changes 3: Simultaneous measures of neuronal activity (implanted electrode or EEG) and fMRI signal changes 4: non-simultaneous measures of neuronal activity (MEG, EEG) and fMRI signal changes, and lastly, 5: Modeling of the hemodynamic response and comparing to precise activation magnitude, timing, or pharmacological manipulations.

In summary, while fMRI is limited somewhat by scanner technology and to a greater degree by the unknowns regarding the spatial, temporal, and magnitude relationships between neuronal activity and hemodynamic signal changes, steady progress is being made in overcoming these limitations. A primary avenue by which the limitations of fMRI can be overcome is that involving integration with other brain activation assessment techniques. The section on Integration will highlight the methodology associated with and some results obtained from fMRI integration.

Integration

Functional MRI data collection and even the experimental process itself can be greatly enhanced in precision, depth, impact, and certainty by effective incorporation of other brain activation assessment techniques ranging from behavioral measures to other imaging techniques (Dale and Halgren, 2001). Techniques that can be simultaneously carried out during time series collection of fMRI data are: 1. behavioral measures such as performance, reaction time, skin conductance, and eye position, 2. EEG, 3. embedded electrodes or multi-electrode arrays, 3. near infrared spectroscopy (NIRS) or optical imaging, 4. Transcranial Magnetic Stimulation (TMS), and 5. physiologic measures such as respiration, heart rate, end tidal CO_2, and skin conductance measures. While simultaneity is desired, it is not required that complementary experimental measures be carried out at the same time in order to be effectively integrated. It is only necessary that they are precisely repeatable. Techniques in which the data are collected before or after fMRI experimentation include of course the above techniques as well as PET and MEG. In this section, the methodology and utility of several of many ways that fMRI experimentation, analysis, and results can be integrated with other modalities are described. Discussed below are behavioral measures, EEG and MEG, TMS, and physiologic measures.

Behavioral Measures:

Behavioral testing has a long history in cognitive neuroscience research. Depending on the hypothesis posed, substantial inferences about brain activity can be made from simple measures of response accuracy and response time. Since the beginnings of fMRI experimentation, a standard procedure has been to collect behavioral measures mostly to ensure that the subject was engaged in the task during the experiment. Subject interface devices such as button boxes or joysticks are typically used. With the onset of rapid event-related fMRI, the ability to selectively average data based on behavioral responses from moment to moment has further increased the range of experiments possible with fMRI.

Two illustrative examples of effective integration of behavioral measures are described. Both of these studies are of processes associated with memory. The methodology of each study differs in the manner in which the behavioral measures are integrated with the fMRI data. In Wagner et al. (Wagner et al., 1998) subjects were presented with lists of words during the time series collection of fMRI data, and the fMRI data was selectively binned based on whether or not the subjects recalled the words after the scanning process. Results revealed that the ability to later remember a verbal experience was predicted by the magnitude of activation in left prefrontal and temporal cortices during that experience.

In Pessoa et al. (Pessoa et al., 2002), fMRI was used to investigate how moment-to-moment neural activity contributed to success or failure on individual trials of a visual working memory task. They found that different nodes of the network involved with working memory were activated to a greater extent for correct compared to incorrect trials during stimulus encoding, memory maintenance during delays, and at test. A logistic regression analysis revealed that the fMRI signal amplitude during the delay interval in a network of frontoparietal regions predicted successful performance on a trial-by-trial basis. Differential activity during the delay periods when working memory was active, occurred even for only those trials in which BOLD activity during encoding was strong, demonstrating that it was not a simple consequence of effective versus ineffective encoding. Their results demonstrated that accurate memory depends on strong sustained signals that span the delay interval of WM tasks. Without precise measures of behavior either after the scanning process (testing for long term memory) or during the scanning process (testing for working memory), these results could not have been achieved.

In general, some of the most insightful fMRI results have resulted from tight integration of moment to moment behavioral measures with time series collection, allowing for selective binning of relevant fMRI data. Other measures have included reaction time, decision processes, eye position, and continuous measures of performance or mental state such as those obtained by the use of a joystick or trackball.

Electroencephalography (EEG) and Magnetoencephalography (MEG)

The signals produced by EEG and MEG are more direct measures of neuronal activity than those produced with fMRI. Both EEG and MEG reflect, respectively, the electric potential and the magnetic field resulting from synaptic currents in neuronal dendrites. Because of the inherently ill-posed "inverse problem" regarding localization of the dipole sources contributing to the electrical potentials and magnetic fields on the surface of the skull, the resolution of EEG and MEG, or rather, the certainty of localization, is generally quite low. Integration of EEG/MEG and fMRI may allow for mapping of brain activity at the spatial resolution of fMRI (effectively "constraining" the inverse problem with MEG and EEG) and the temporal resolution of ms that is afforded by MEG and EEG. This will be discussed in more detail when describing MEG integration below. Also, simultaneous use of EEG with fMRI can enhance the ability for fMRI to map spontaneous and transient processes only detectible by EEG but mappable using hemodynamic responses that occur 3 to 10 seconds after a signature EEG response.

The complementary use of EEG and fMRI is a bourgeoning field in itself. Since 1997, over 200 papers have been published on this topic alone. A primary use of simultaneous EEG and fMRI data collection is for the accurate measurement of hemodynamic changes associated with spontaneously occurring and transient events that are measurable with EEG. (Lemieux, 2003). Another use of these simultaneous measures has been to better understand the neuronal correlates of fMRI – comparing the time-locked averaged evoked response characteristics with the hemodynamic response characteristics. The latter experiment does not require simultaneous EEG and fMRI but the results derived with simultaneous acquisition are likely to be more accurate since no experiment is replicated perfectly inside and outside of the scanner.

A promising avenue by which simultaneous fMRI and EEG may be used clinically is towards the more accurate localization of epileptic foci. In specific clinical populations, these foci exhibit spontaneous, irregular EEG activity. The use of simultaneous EEG and fMRI allows for functional images to be selectively averaged based on when this signature activity occurs.

Another unique application of EEG and fMRI is to determine the neuronal correlates of spontaneously changing brain activity associated with specific EEG frequencies. The basic experiment is to simultaneously measure EEG and fMRI. During subsequent data processing, the power spectrum of the EEG traces is created for each TR period. The amplitude of the power spectrum at a specific frequency range (for example, alpha frequencies: 8-12 Hz, and beta frequencies: 17-23 Hz) at each TR is then convolved with a hemodynamic response function and used as a regressor in fMRI time series analysis. Using this approach, Goldman et al (Goldman et al., 2001) and Laufs et al (Laufs et al., 2003b, Laufs et al., 2003a) have been able to accurately map regions that exhibit changes that are correlated with spontaneous changes in oscillatory activity.

Simultaneous use of EEG and fMRI data is challenging because the collection of EPI data creates a substantial artifact in the EEG trace whenever magnetic field gradients are applied. Filtering out this artifact has been achieved by several strategies including those that include simple discarding of EEG points that occur during image collection, hardware-based filters, more sophisticated post processing techniques, and what is known as spike triggered fMRI scanning in which unique EEG activity (i.e. spiking) triggers the scanner to collect images.

Efforts to integrate MEG and fMRI (Dale and Halgren, 2001) have begun to increase as MEG systems become more available, and as the interpretive limits of fMRI alone become more apparent. MEG and fMRI data cannot be collected simultaneously, therefore the effectiveness of the integration relies on precise experimental replicability. Another highly challenging but potentially promising method by which MEG (or EEG) and fMRI can be integrated is for fMRI activation maps to be used to help the process by which dipole locations are determined. The potential information gained by this procedure is significant in that if the dipole sources for a given cognitive process are precisely determined, then the inverse problem can be replaced by a much more readily solvable forward problem. Starting with the dipole locations, the relative dynamics of measured fields at the surface of the skull can then be used to infer the dipole source timings with ms accuracy (Ahlfors et al., 1999).

While the promise of constraining dipole sources using fMRI data is exciting, many problems remain. First, if there exist mismatches between fMRI activation foci and the true dipole sources, substantial errors in timing estimates will be generated. In this sense, the timing estimation is quite "brittle" in that any errors in dipole estimation render the results almost uninterpretable. Growing evidence exists that there are, in fact, substantial differences between fMRI activation maps and MEG visible dipole sources. With MEG, opposing dipoles may cancel each other, rendering their effects invisible to fMRI. With fMRI, false positives are ubiquitous in individual data, and, likewise, it is not certain whether all MEG sensitive effects contribute to hemodynamic changes. Also, cognitive tasks typically involve highly distributed networks within and across distributed regions which generally defy simplification to a set of dipoles. Currently, effort is being made towards estimating the certainty of the dipole sources, therefore increasing the flexibility and robustness of this approach.

A central issue in the integration of fMRI and EEG/MEG data, and more generally, the interpretation of fMRI signal changes, is that of clarifying the relationship between neuronal activity and fMRI signal changes. Substantial effort has been applied using other modalities to better understand fMRI contrast. Examples representing only a small fraction of this effort, include those involving MEG (Singh et al., 2002), EEG (Horovitz et al., 2002), optical imaging (Grinvald et al., 2000, Villringer, 1997, Cannestra et al., 2001, Boas et al., 2004), electrophysiologic recording in humans (Huettel et al., 2004) and animal models (Logothetis et al., 2001, Duong et al., 2000, Devor et al., 2003) and microscopic oxygen probes in animal models (Thompson et al., 2003, Thompson et al., 2004) have begun to reap benefits.

Transcranial Magnetic Stimulation (TMS)

TMS involves the use of a highly localized, rapidly oscillating magnetic field directed at specific circuits of the brain. This rapid oscillation induces neuronal activity, thereby disrupting normal function for what is thought to be a very brief period of time. The power of this technique is in the fact that it can probe the necessity of specific nodes in a network as they relate to specific processes. This technique is highly complementary to brain mapping techniques in that a central problem in the interpretation of brain activation maps is that of determining causality. Information in a map may contain a network of activation, but it is not apparent from this map which nodes of this network are activated as a result of the task or are activated in order to perform the task. Because TMS allows for specific nodes of this network to be temporarily disabled, observation of behavior associated with the application of TMS can tease apart the causality of the network involved (Lomarev et al., 2000). The additional dimension of neuronal timing can also be explored by modulation of TMS application time relative to stimulus and response timing. Typically, the TMS timing is titrated to determine the interval which most effectively interferes with a specific behavioral process, thereby revealing neuronal communication rates.

Practically, with TMS and fMRI integration, a brain activation map is first produced and subsequently used to guide TMS stimulation outside of the scanner. Nevertheless, some groups have been able to perform TMS during collection of fMRI time series data to probe the effects of TMS in itself, on brain activation, thereby assessing functional connectivity with the assumption that if one node is activated, then the nodes that it is functionally associated with will also be activated. Performance of

TMS during fMRI has been achieved (Bohning et al., 2000b, Bohning et al., 2000a). This application is highly challenging, and perhaps risky, since the torque generated by interaction of the strong electrical currents of TMS device (typically a figure eight loop of wire) with the scanner magnetic field can be substantial, depending on the orientation (Bohning et al., 2003).

Because TMS devices are relatively inexpensive and easy to implement, and currently understood to be relatively non-invasive, this technique is growing rapidly in popularity as the information that it provides is highly complementary to the data provided by fMRI.

Physiologic Measures

Lastly, a growing trend in fMRI data collection has been towards not only simultaneous recording of behavioral responses but also simultaneous collection of physiologic measures such as heart and respiration waveforms, end tidal CO_2, and skin conductance. The information gleaned from these measures range from assessment and reduction of artifactual influences on the BOLD response to assessment and use of measures of arousal and attention.

Respiration and cardiac pulsations are known to contribute to artifactual signal changes in fMRI, either from changes in the magnetic field caused by the chest cavity movement (respiration) (Windischberger et al., 2002, Pfeuffer et al., 2002a) or by localized acceleration of blood, cerebral spinal fluid, and brain tissue (cardiac pulsations) (Dagli et al., 1999). Simple recording of respiration using a chest bellows and of cardiac pulsation using a pulse oximeter can allow these artifactual waveforms to be used as a "nuisance" regressors thereby effectively increasing functional contrast to noise and reducing false positive results.

A challenge in removing cardiac effects is that the TR is typically too low to sample the cardiac waveform sufficiently. Methods have been proposed to work around this problem (Frank et al., 2001, Menon, 2002, Noll et al., 1998). For some fMRI studies, the movement artifacts caused by cardiac pulsations, particularly at the base of the brain, are prohibitive – particularly when attempting to image very small structures that may displace several voxels with each cardiac cycle. A novel method involving cardiac gating, and subsequent correction of T1 related fluctuations from irregular TR values has been implemented – effectively solving this problem (Guimaraes et al., 1998).

Ongoing studies of spontaneous end-tidal CO_2 fluctuations have revealed useful information about the nature of BOLD time series fluctuations (Wise et al., 2004). Maps generated using spontaneous changes in end tidal CO_2 appear to delineate the spatial distribution of resting state venous blood volume (indicating the voxel-wise potential for BOLD signal changes). This study also gives strong evidence that simple changes in breathing rate and depth during an experiment can influence BOLD signal changes.

These above measures have a potentially complementary impact on the expanding research on resting state fluctuations focused at understanding functionally correlated resting networks (Lowe et al., 1998, Gusnard et al., 2001, Biswal et al., 1995).

Skin conductance measures have also been successfully obtained during the collection of fMRI time series data (Critchley et al., 2000, Patterson et al., 2002, Williams et al., 2000, Shastri et al., 2001). Skin conductance is a sensitive measure of such states as arousal, attention, and anxiety. The use of this concomitant skin conductance time series information in the context of fMRI has been along two avenues. First, this has been used to ensure that the subjects are exhibiting the appropriate response to specific stimuli. Figure 5 shows time course plots from an experiment that involved conditioning a subject to expect a shock when they hear a tone presented during the conditioned stimulus (CS) period (Knight et al., in press). The subject controls a dial according to subjective expectation level. The subject's skin conductance is also continuously measured (SCR).

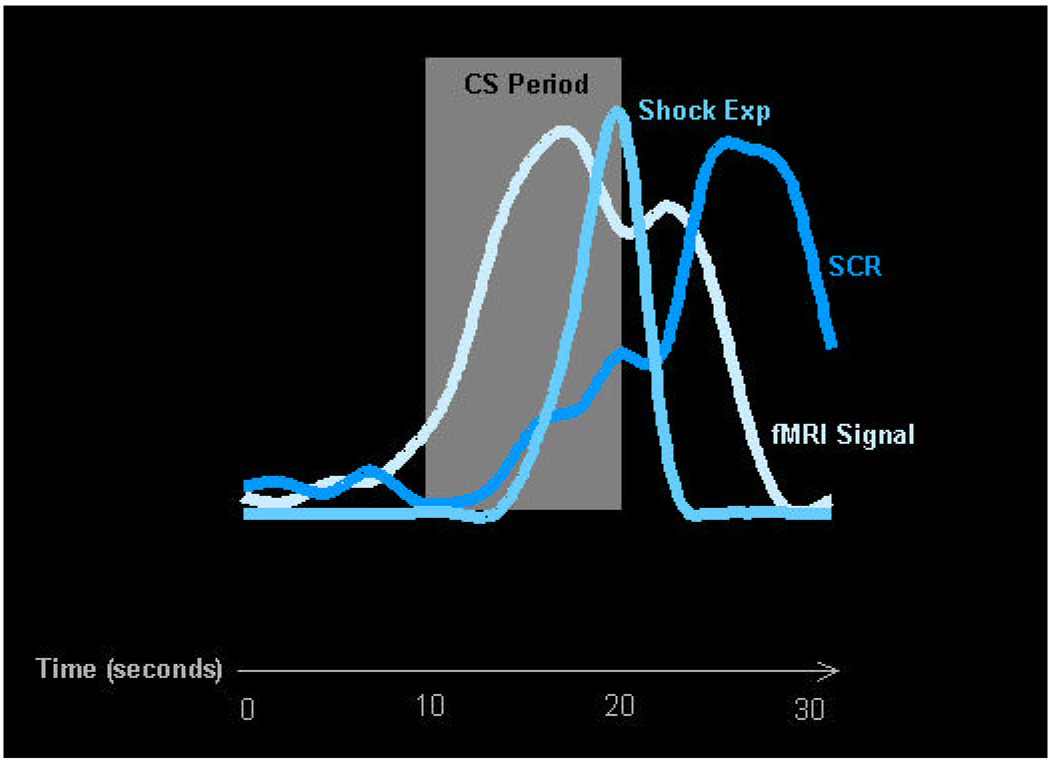

Figure 5: This set of time course plots is an example of the type of information that can be obtained simultaneously during fMRI time course collection to help guide experimental analysis and interpretation. This particular experiment involved conditioning a subject to expect a shock when they hear a tone during the conditioned stimulus (CS) period. The subject controls a dial according to subjective expectation level. The subject's skin conductance is also continuously measured (SCR). (Figure provided courtesy of David Knight, Ph.D., Section on Functional Imaging Methods, NIMH)

A second way that simultaneous measures of skin conductance are used is in much the same way as simultaneous EEG has been used. The correlation of the SCR time course can be calculated with fMRI time series data to demonstrate the neuronal correlates of skin conductance in specific mental states or during resting state. An example of this type of study is by Patterson et al. (Patterson et al., 2002) They measured spontaneous skin conductance changes continuously during resting state and specific tasks. Using the spontaneous skin conductance measurement as a regressor, they identified a specific set of regions that showed activity that was correlated with skin conductance changes independent of the task being performed.

Conclusion:

This chapter represents only a grainy snapshot of a rapidly changing scene. An attempt was made to give a perspective of the history, development, limits, some of the most innovative ideas, and general excitement surrounding fMRI, which by all measures is advancing rapidly in sophistication and impact. Integration of fMRI with other techniques is steadily contributing to our understanding of how the human brain is organized, how it changes from moment to moment and year to year, and how it varies across clinically relevant populations. While the ultimate impact that fMRI will have on the fields of neuroscience and medicine is still too early to tell, it is clearly evident that it is a maturing technique with considerable potential.

Further Information

MRI and fMRI Basics:

- ?? http://www.simplyphysics.com/MAIN.HTM
- ?? http://defiant.ssc.uwo.ca/Jody_web/fmri4dummies.htm

Processing Software:

- ?? http://afni.nimh.nih.gov/afni

Analysis of Functional NeuroImages by Bob Cox, NIMH.

- ?? http://www.bic.mni.mcgill.ca/software/

from the Brain Imaging Center at McGill University

- ?? http://grommit.lrdc.pitt.edu/fiswidgets/

a Java graphical user interface for a number of neuroimaging analysis packages

- ?? http://brainmapping.loni.ucla.edu/BMD_HTML/SharedCode/SharedSoftware.html

general analysis tools from UCLA brain imaging center

- ?? http://www.mayo.edu/bir/Software/Analyze/Analyze.html

from the Mayo Clinic

- ?? http://www.brainvoyager.com/

a commercial product from Brain Innovation: Rainer Goebel

- ?? http://www.math.mcgill.ca/keith/fmristat/

a set of useful Matlab programs: Keith Worsley

- ?? http://www.fmrib.ox.ac.uk/fsl/

a comprehensive set of analysis programs: Steve Smith, Oxford University

Books:

?? Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques, by Richard Buxton, Cambridge University Press, 2001

?? Functional Magnetic Resonance Imaging, by Scott A. Huettel, Allen W. Song, and Gregory McCarthy, Sinauer Associates, 2004.

?? Functional MRI: An Introduction to Methods, (Eds Peter Jezzard, Paul M. Mattthews, and Stephen M. Smith), 2003.

?? Functional MRI, (Eds. Chrit Moonen and Peter A. Bandettini), Springer-Verlag, 1999.

?? Functional MRI: Basic Principles and Clinical Applications, (Eds. Scott H. Faro, and Feroze B. Mohamed), Springer-Verlag, 2005.

Functional MRI Course Websites:

?? http://www.nmr.mgh.harvard.edu/fmrivfp/

?? http://www.firc.mcw.edu/course/

Organizations:

?? http://www.cogneurosociety.org/

The Cognitive Neuroscience Society

?? http://www.humanbrainmapping.org/

The Organization for Human Brain Mapping

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